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Review Article

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Immunological and physiological responses related to orthodontic treatment

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ABSTRACT

Orthodontic treatment is usually approached to achieve better aesthetics by influencing tooth movement in different positions within the jaw. The application of mechanical forces during the process of treatment is the main responsible for these events. Remarkable changes in the vascularity of the underlying tissues were also reported to occur secondary to applying orthodontic forces. This significantly leads to the synthesis and release of many metabolites and signaling molecules. Furthermore, it might be associated with various immunological and physiological responses that enhance or deteriorate the prognosis. Therefore, the present study reviewed the literature to identify the different immunological and physiological responses secondary to orthodontic treatment. Our findings indicate that different immune cells and immunoglobulins are usually involved in orthodontic treatment-related events. Moreover, we found that cytokines and chemokines have an important role in the post-treatment inflammatory process, leading to bone resorption or bone formation. Various cytokines were reported in this context, including TNF- α , IFN- γ , IL-13, IL-12, IL-8, IL-6, and IL-1 β . The roles of these modalities have been discussed based on their effects on bone remodeling following orthodontic treatment.

Keywords: Inflammation, Immunological, Physiological, Orthodontic, Treatment

INTRODUCTION

It is widely known that orthodontic treatment is a multistep approach that is usually associated with various cellular and molecular events within the periodontium, including the periodontal ligament, gingiva, cementum, and alveolar bone. In addition, it is usually approached to achieve better aesthetics by influencing tooth movement in different positions within the jaw.^{1,2} The application of mechanical forces during the process of treatment is the main responsible for these events. Moreover, it has been reported that the alveolar bone and periodontal ligaments are the main structures responsible for secondary bone remodeling.³

Remarkable changes in the vascularity of the underlying tissues were also reported to occur secondary to applying orthodontic forces. This significantly leads to the synthesis and release of many metabolites and signaling molecules. These substances are linked to significant physiological and immunological responses around the targeted dental tissues leading to favorable microbiological effects and better prognosis.^{4,5} In this context, evidence showed that many physiological and immunological mechanisms are

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involved in the process of orthodontic treatment. 1,2 The aim of the study was to discuss the different physiological and immunological mechanisms following orthodontic treatment based on evidence from studies in the literature.

METHODS

This literature review was based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 15th November 2021 using the Medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing potential studies, a further manual search for papers was done through Google scholar while the reference lists of the initially included papers. Papers discussing immunological and physiological responses related to orthodontic treatment were screened for useful information. No limitations were posed on date, language, age of participants, or publication type.

DISCUSSION

Many previous studies in the literature have evaluated the physiological and immunological responses concerning orthodontic treatment events. As a result, different events were reported, including the abundant presence of immune modulators, inflammatory cytokines, and immunoglobulins. In the present section, we will discuss these different factors and their roles based on the findings from previous investigations. Abbas et al concluded that breaking immunological tolerance can be significantly achieved by the presence of a state of chronic inflammation.⁶

This has been attributed to the facilitated presentation of the different autoantigens to the immune cells. It has been furtherly demonstrated that orthodontic teeth movement has been associated with a remarkable migration of different immunocompetent and non-specific cells, including antigen-presenting cells, plasma cells, lymphocytes, and immunoglobulins. Feidence also indicates that bone destruction has been observed secondary to orthodontic treatment due to the immune response of B and T lymphocyte modulation. A previous study also demonstrated that susceptible patients might furtherly suffer from suppressed humoral and systemic immune responses to the different dentine antigens. 10 Exposing the dentin matrix and damaging the cementum layer might develop secondary to the development of hyaline necrosis and compression areas during orthodontic treatment.11

An autoimmune response against dentin matrix proteins was also reported to develop during orthodontic treatment potentially. This has been shown among patients with traumas and root resorption that have unprecedented levels of anti-dentin antibodies. ¹¹⁻¹³ The presence of antibodies against various dentin antigens was also reported to influence IgM and IgG levels, reducing the former's levels

and increasing the latter's levels among patients with pathological root resorption. This indicates that an autoimmune response significantly develops secondary to orthodontic treatment.

Evidence shows that fixed and removable orthodontic significantly appliances can influence immunogenicity, leading to the abundant release of the different immune cells and modulators. Previous studies also indicated that Secretory immunoglobulin A (SIgA) serum levels are associated with orthodontic treatment. 14,15 For example, Taha et al reported that increased levels of IgA and IgG and reduced levels of IgM were more significant among patients wearing orthodontic appliances than other patients that do not wear them. ¹⁶ Besides, these levels were correlated with the severity of root resorption among the included population. Similar findings were also reported in another study by Abbas et al.⁶

Hidalgo et al indicated that low levels of IgM and high levels of IgG were reported following orthodontic treatment and induction of pathological root resorption, indicating the significance of these molecules in the primary immune response against dentin antigens. 12 Oral secretory immunity was also reported to be associated with wearing removable orthodontic appliances. After orthodontic treatment by 3-6 months, it has been evidenced that there are abundant amounts of SIgA in the affected patients. It should be noted that evidence shows that the levels of these compounds were higher among patients with fixed orthodontic treatment than patients with removable appliances. This might be attributed to the potential ability of these modalities to reduce oral hygiene, leading to a significant alteration in oral homeostasis and microflora. 17-19

The correlation between adaptive and innate immunity primarily determines the oral immune response. Initiating cellular immunity has been associated with adaptive immunity response. Evidence shows that T lymphocytes play a vital role in the development of these mechanisms. ¹⁰ Furtherly reported, T cells play an essential role in regulating immune response during orthodontic treatment. ²⁰ This is because tissue remodeling is an essential process to perform successful orthodontic treatment. It has been evidenced that various migratory and local cells take part in these processes, including bone surface lining cells and fibroblasts. ²⁰⁻²²

Previous studies also demonstrated that during orthodontic treatment, specific immunocompetent cells migrate to the periodontal ligament. These cells include antigenpresenting cells (dendritic cells and macrophages), plasma cells, and lymphocytes. Para These cells also have an essential role in modulating the impact of mechanical forces in dentin-related structures. Various cells have been reportedly involved in remodeling, including immune cells, chondrocytes, cementoblasts, odontoblasts, osteoclasts, osteocytes, osteoblasts, and fibroblasts. The periodontal ligament and bone marrow infiltration by

inflammatory cells (dendritic cells and macrophages) were also reported secondary to orthodontic treatment. 24-26 These cells remarkably modulate T-cell-mediated immune response. Accordingly, it has been concluded that lymphocytes can significantly participate in the process of alveolar bone remodeling secondary to orthodontic treatment. A previous investigation also demonstrated that inflamed gingival tissues have abundant amounts of neutrophils and macrophages. 27

During orthodontic treatment, it has been shown that different chemokines and cytokines are upregulated and take part in various physiological responses during these settings. Chemokines are cells that can attract other immune and inflammatory mediators to the local site of inflammation.^{3,23,28} Evidence shows that the presence of these cells during orthodontic treatment has been associated with significant stimulation of precursor and inflammatory cells to be recruited from the related blood vessels into the extravascular space. Moreover, it has been shown that they remarkably facilitate the expression of adhesion molecules in these settings. It has been shown that monocyte chemoattractant protein-1 is one of the commonest compounds released during orthodontic treatment.^{29,30} Evidence shows that this protein has an essential role in recruiting monocytes. In addition, the levels of osteoclasts and macrophages were reported to increase secondary to the infiltration of the dental structures by these molecules from the related microvasculature. Osteoclastic release and activation have also been reported secondary to tissue infiltration by different chemokines. ^{29,30} Therefore, it has been concluded that chemokines are vital in bone tissue remodeling secondary to orthodontic treatment application forces. 1,31

The role of cytokines in orthodontic treatment has also been previously established among different studies in the literature. These compounds have been essential in the various physiological and inflammatory responses during orthodontic treatment. They are extracellular signaling proteins that facilitate apoptosis, activation, and cellular differentiation within periodontal ligaments and bone tissues. Evidence shows that the main functions of cytokines include anti-inflammatory and proinflammatory mechanisms that are directly correlated with the secondary physiological responses during orthodontic treatment. ^{32,33}

The essential role of anti-inflammatory cytokines is to have an inhibitory effect. By such mechanisms, these cytokines can remarkably control bone resorption and inflammation.³³ However, it has been shown that secondary to the inflammatory process, tension forces usually influence the release and synthesis of different cytokines, including Interleukin-10 (IL-10). Previous research also demonstrated that IL-10 and IL-8 are extensive amounts in the periodontal ligament during orthodontic teeth movement.^{4,34} Furthermore, these compounds have been linked to the inhibition of bone resorption and osteoclastogenesis. It was also previously shown that cytokine mediators can inhibit the production

of (or negatively influence the synthesis and release of) Tumor necrosis factor- α (TNF- α), IL-1, and IL-6. 32,35,36 The release of anti-inflammatory cytokines was also reported to interfere with osteoclast differentiation by significantly stimulating osteoprotegerin synthesis. Secondary to these events, evidence indicates that bone resorption is significantly lower than the deposition rate. 32,35 Inhibition of osteoclastogenesis was also previously evidenced in the literature to be mediated by osteoblasts. These cells produce significant anti-inflammatory cytokines, including osteoprotegerin and IL-10, essential in bone formation. 37

Various proinflammatory cytokines were reported to be produced following orthodontic treatment. These cytokines are released from the periodontal ligament and related immune cells. Some of the detected cytokines include TNF-α, IL-13, IL-12, IL-8, IL-6, and IL-1β.34 Krishnan and Davidovitch also reported other proinflammatory cytokines, including Interferon-gamma (γ-IFN), IL-8, IL-3, and IL-2.⁴ Evidence shows that the presence of anti-inflammatory mediators and cytokines have been associated with a significant reduction in tooth movement during orthodontic treatment. Therefore, it has been concluded that proinflammatory cytokines are usually associated with increased tooth movement. 30,38 Evidence shows that three main cytokines, including TNFα, IL-6, and IL-1β, are involved in the process of bone remodeling and regulation. 20,39,40

Various systemic and local physiological changes have been correlated to these cytokines, indicating the development of acute inflammation. It has been further demonstrated that the gingival crevicular fluid analysis shows a significant increase in these cells following orthodontic treatment. The abundant increase in these cells has been extensively evidenced in the literature as an essential part of the physiological response of periodontal tissues secondary to the application of orthodontic treatment mechanical forces. Evidence shows that the increased levels of these cytokines usually begin at the 12th-24th hours following orthodontic treatment. These events are usually associated with other cells, like fibroblasts and leukocytes of alveolar bone, periodontal ligament, and gingival tissue. It

The levels of TNF- α , IL-6, and IL-1 β peak within three days following the application of mechanical forces of orthodontic treatment. They are usually released locally at the site of tissue inflammation and significantly lead to the development and initiation of the bone resorption process. Therefore, these substances are usually referred to as osteotropic cytokines. Evidence also indicates that osteoclasts synthesis and release are associated with TNF- α and IL-1 β . Accordingly, it has been evidenced that inflammatory mediators lead to the release of these proinflammatory cytokines. In this context, bone resorption occurs secondary to the activation of osteoclasts by the released cytokines. In addition, evidence shows that

IL-1β has various pleiotropic effects during orthodontic treatment. Therefore, it is considered one of the most important cytokines in these settings. Similar local and systemic biologic effects were also noticed with IL-1. The reported physiological effects include inhibition of bone formation and influencing bone resorption secondary to the significant stimulation of osteoblasts, osteoclasts, endothelial cells, and fibroblasts, in addition to attracting leukocytes.

The production of type 1 T-helper cells was also reported to occur secondary to the release of IFN- γ . However, evidence regarding their physiological activities during orthodontic treatment is controversial. A previous study reported its potential role in bone remodeling following orthodontic treatment. ²³ In addition, it has been reported to influence the levels of other cytokines, like TNF- α and IL-1. The release of nitric oxide was also reported to increase following the increased levels of cytokines. ²³ Nitric oxide has been reported to enhance osteoclast-osteoblast coupling. Apoptosis of T-helper cells might also occur secondary to IFN- γ , leading to bone resorption. ^{4,32}

Alveolar bone resorption was also reported to occur secondary to other mediators including IL-11, and IL-8.32,38 Thus, evidence shows that the different cytokines might have synergistic effects (by acting with each other) or might act solely to produce the inflammatory process, sufficient to produce bone anabolism and resorption. A previous study furtherly reported that IL-8 and IL-2 triggered bone remodeling in the periodontal ligament. These factors indicate the development of physiological responses secondary to orthodontic treatment. 27,33

CONCLUSION

Orthodontic treatment might be associated with various immunological and physiological responses that might enhance or deteriorate the prognosis. Therefore, the present study reviewed the literature to identify the different immunological and physiological responses secondary to orthodontic treatment. Our findings indicate that different immune cells and immunoglobulins are usually involved in orthodontic treatment-related events. Moreover, we found that cytokines and chemokines have an important role in the post-treatment inflammatory process, leading to bone resorption or bone formation. Various cytokines were reported in this context, including TNF- α , IFN- γ , IL-13, IL-12, IL-8, IL-6, and IL-1 β . The roles of these modalities have been discussed based on their effects on bone remodeling following orthodontic treatment.

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